A Pilot Study of the Feasibility of Prehospital Delivery of Remote Ischemic Conditioning by Emergency Medical Services in Chest Pain Patients

(A Study of the Feasibility of Prehospital Remote Ischemic Conditioning)

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Principal Investigator & Regulatory Sponsor:	Mehul D. Patel, PhD Research Assistant Professor Department of Emergency Medicine University of North Carolina at Chapel Hill 170 Manning Drive, CB #7594 Physicians Office Building, 1st Floor Chapel Hill, NC 27599-7594 Email: mehul_patel@med.unc.edu Phone: (919) 843-7307
Co-Investigators:	Timothy F. Platts-Mills, MD, MSc Assistant Professor and Vice Chair of Research Department of Emergency Medicine University of North Carolina at Chapel Hill Joseph M. Grover, MD Clinical Assistant Professor Department of Emergency Medicine University of North Carolina at Chapel Hill Medical Director of Orange County Emergency Services Joseph S. Rossi, MD, MSCI Clinical Associate Professor and Director of Interventional Cardiology Division of Cardiology University of North Carolina at Chapel Hill
Funding Sponsors:	The North Carolina Translational and Clinical Sciences Institute University of North Carolina at Chapel Hill 160 N. Medical Drive, CB #7064 Brinkhous-Bullitt Building, 2nd Floor Chapel Hill, NC 27599-7064 Department of Emergency Medicine University of North Carolina at Chapel Hill 170 Manning Drive, CB #7594 Physicians Office Building, 1st Floor

Chapel Hill, NC 27599-7594

Study Product:	autoRIC® Device CellAegis Devices, Inc. 139 Mulock Avenue, 1st Floor Toronto, Ontario M6N 1G9
Protocol Number:	N/A
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UNC IRB Number:	17-0287 (approval pending)

Table of Contents

List of Abbreviations

AE	Adverse event
ALS	Advanced life support
CABG	Coronary artery bypass graft
CI	Confidence interval
CRF	Case report form
ECG	Electrocardiogram
ED	Emergency department
EMS	Emergency medical services
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ID	Identifier
IDE	Investigational device exemption
IEC	International Electrotechnical Commission
IRB	Institutional Review Board
LED	Light-emitting diode
MI	Myocardial infarction
NIH	National Institutes of Health
OCES	Orange County Emergency Services
PCI	Percutaneous coronary intervention
PHI	Protected health information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
RIC	Remote ischemic conditioning
RCT	Randomized controlled trial
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Study coordinator
STEMI	ST-segment elevation myocardial infarction
TraCS	Translational and Clinical Sciences
UNC	University of North Carolina

Study Summary

Title	A pilot study of the feasibility of prehospital delivery of remote ischemic conditioning by emergency medical services in chest pain patients
Short Title	Prehospital RIC Pilot Study
Protocol Number	N/A
Phase	Pilot
Methodology	Open label; Non-randomized; Single-arm
Study Duration	12 months
Study Center(s)	Single-center
Objectives	To assess the feasibility of the delivery of RIC by EMS in the prehospital setting by evaluating the following: Primary outcome – Duration of RIC administered Secondary outcomes – Enrollment rates and protocol efficiency; paramedic acceptability of protocol; and patient tolerability of RIC
Number of Subjects	50
Diagnosis and Main Inclusion Criteria	Patients experiencing a recent onset of chest pain or anginal equivalent symptoms requiring emergency medical services (suspected ST segment-elevation myocardial infarction patients will be excluded)
Study Product, Dose, Route, Regimen	The autoRIC® Device; an upper arm cuff will automatically alternate 5 minutes inflated at 200 mm Hg and 5 minutes deflated for a total of 4 cycles (total 40 minutes)
Duration of administration	40 minutes (4 cycles at 10 minutes each)
Reference therapy	No comparison therapy
Statistical Methodology	Descriptive statistics (e.g., proportions, medians) will be computed to summarize primary and secondary outcomes. Where appropriate, point estimates will be presented along with 95% confidence intervals. No inferential statistical tests will be performed. Qualitative data will be analyzed using mixed methods approaches.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

A myocardial infarction (MI), otherwise known as a heart attack, occurs when obstruction of a coronary artery causes sudden loss of blood flow to the heart muscle. If blood flow is not restored (reperfusion) within the first few hours, the lack of oxygen supply (ischemia) results in irreversible myocardial injury and eventually necrosis of heart tissue (infarction). Depending on the extent of tissue damage, or myocardial infarct size, the individual may die or suffer long-term disabilities. In the U.S., there are ~750,000 MIs each year and ~117,000 related deaths, making it a leading cause of morbidity and mortality.[1] Furthermore, the annual health care costs of myocardial infarction in the U.S. are projected to exceed $300 billion by 2030.[1,2]

Prompt reperfusion with emergency coronary stent placement, or primary percutaneous coronary intervention (PCI), substantially reduces myocardial injury and improves clinical outcomes; primary PCI is therefore the preferred treatment for many acute MI patients.[3] However, reperfusion can paradoxically induce further myocardial damage.[4] This ischemia-reperfusion injury can account for up to 50% of the final infarct size in patients with MI following reperfusion.[5] While primary PCI is now the standard of care in the US and other developed countries, therapies to protect against ischemia-reperfusion injury remain investigational.[5,6]

Remote ischemic conditioning (RIC) is a non-pharmacological and non-invasive therapy for acute MI whereby intermittent, brief episodes of benign ischemia and reperfusion are induced by inflating and deflating a standard blood pressure cuff on the upper arm or leg.[7] This therapy is hypothesized to protect against ischemia-reperfusion injury by cellular signaling between the remote site (limb) and the target organ (heart) through humoral or neuronal protective signal transfer.[8,9] Although the mechanisms of RIC are unclear, it is thought to target several mediators of ischemia-reperfusion injury and may therefore be a more effective therapeutic strategy than those that target a single pathway.[5,10]

1.2 Investigational Device

The autoRIC® (CellAegis Devices, Inc., Toronto, Ontario) is the only automated device currently available to deliver RIC for acute conditions.[11,12] With timed inflations and deflations of an arm cuff, it automatically delivers four RIC cycles of five minutes of pressure at 200 mm Hg followed by five minutes of no pressure for a total 40-min treatment period. The autoRIC® has CE Mark certification in Europe and Health Canada approval to administer RIC therapy in adult patients with acute MI and those undergoing cardiothoracic interventions or surgery; the device is however limited to investigational use in the U.S. (http://www.cellaegisdevices.com/product.html accessed May 9, 2017).

Figure 1. CellAegis' autoRIC® Device

The autoRIC® system (Figure 1) consists of a rechargeable, reusable control unit that clicks into a one-time use, disposable applicator cuff and inflates and deflates the cuff to a preset pressure of 200 mm Hg on a timer. The applicator cuffs come in three adult sizes to accommodate arm circumferences ranging from 22 to 44 cm. A stand-alone charger for the control unit uses a standard AC adapter and can be wall mounted. The autoRIC® is compliant with international safety and

performance standards for medical devices and electrical equipment including particular requirements for automated non-invasive sphygmomanometers (IEC 80601-2-30:2009).

1.3 Preclinical Data

In 1986, Murry et al. first described ischemic conditioning in dogs, in which four 5-min occlusions of the circumflex coronary artery separated by 5-min episodes of reperfusion before a sustained occlusion limited myocardial infarct size to 25% of that observed in the control group.[13] Dickson et al. demonstrated *remote* ischemic conditioning reduces infarct size with the transfer of coronary effluent from a preconditioned donor rabbit heart to an acceptor rabbit heart by transfusion.[14] In 2002, Kharbanda et al. showed transient lower limb ischemia (four 5-min cycles) in pigs prior to a myocardial infarction substantially reduced infarct size.[15] These researchers also demonstrated that the RIC response could be induced in humans non-invasively by simply inflating a standard blood pressure cuff around the upper arm to 200 mm Hg of pressure with three cycles of five minutes inflated and five minutes deflated. These and other preclinical studies provide convincing evidence of the existence of ischemia-reperfusion injury and suggest that ischemic conditioning has significant promise to prevent lethal reperfusion injury in humans.[5,9]

1.4 Clinical Data to Date

Prior randomized controlled trials (RCTs) have shown the benefit of RIC in several clinical applications, including reducing myocardial and renal injury in patients undergoing coronary artery bypass graft (CABG) surgery, abdominal aortic aneurysm surgery, and elective PCI.[16-20] However, some clinical studies found null findings with RIC in these settings. Possible explanations for these null findings include differences in study design, inclusion criteria, and concomitant medications that could mitigate the effects of RIC.[21] Recently, two large multi-center RCTs, conducted in the United Kingdom and Germany, failed to show a benefit of RIC on clinical outcomes. Garratt, et al. suggest one possible reason for the lack of clinical efficacy of RIC in recent large multi-center RCTs in patients undergoing *elective* CABG surgery[22,23] is that the anesthetic drug propofol may inhibit signal transduction in response to the remote ischemia.[24] They, among others, call for further clinical investigations in populations that may derive the most benefit from RIC, namely acute ST-segment elevation myocardial infarction (STEMI) patients undergoing *emergent* PCI.[24,25]

Existing evidence on clinical efficacy suggests RIC is a promising adjunct to PCI in STEMI patients. Botker et al. conducted a randomized trial of RIC administered in the prehospital setting among 333 STEMI patients in Denmark, in which they found RIC was feasible to implement in the ambulance and safely improved myocardial salvage 30 days after PCI.[26] In a subgroup of left anterior descending STEMIs, myocardial salvage further increased, and left ventricular function was also significantly improved at 30 days.[27] Two smaller randomized studies in STEMI patients undergoing primary PCI found RIC had beneficial effects on ST-segment resolution, cardiac enzymes, and other intermediate outcomes.[28,29]In a post hoc analysis of the Danish trial, Sloth et al. found the RIC plus PCI group, compared to PCI only, had half the 4-year risk of the primary composite endpoint of major adverse cardiovascular events including all-cause mortality (HR=0.49, 95% CI 0.27-0.89).[30] A recent meta-analysis synthesized results from four randomized studies that reported clinical endpoints and found major cardiovascular risk was significantly lower in patients receiving RIC + PCI compared PCI only (RR=0.57, 95% CI 0.40-0.82).[31] Patient recruitment is underway for two large, multi-center clinical efficacy trials of RIC, administered with the autoRIC® device, in STEMI patients undergoing primary PCI (CONDI2 NCT01857414 and ERIC-PPCI NCT02342522). However, even if these European and UK trials establish the efficacy of RIC in these patients, further U.S.-based research will be necessary to demonstrate effectiveness and facilitate implementation in U.S. emergency cardiac care systems.

1.5 Study Rationale

Emergency medical services (EMS) play a key role in regional systems of STEMI care in the U.S. With proper training and patient care protocols, paramedics can perform and interpret 12-lead electrocardiogram (ECG) for STEMI in the field and directly transport suspected STEMI patients to a PCI-capable hospital, which has been shown to reduce delays to treatment and improve outcomes.[32-34] Based on the findings from the Danish trial, EMS is a promising setting for field administration of RIC in acute MI patients prior to hospital arrival. There are however important differences in the provision of EMS between European countries like Denmark and the U.S. While EMS care in European countries is often provided by emergency physicians and have a culture of treating patients at the scene, ambulances in the U.S. are staffed with paramedics who are trained to prioritize timely transport to the hospital.[35-37] Additional U.S.-based research of RIC is needed to elucidate the influence of these personnel and system factors and inform design decisions for future U.S.-based clinical studies that build on the completed trial from Denmark and the other European trials currently underway.

A recent feasibility study of administering RIC in patients with STEMI during U.S. air medical transports showed 84% of patients had at least three cycles of RIC completed.[38] In this multi-state region, the air medical crew was typically a paramedic and nurse team, which made timed, manual cuff inflations and deflations feasible. However, the vast majority of acute MI patients in the U.S. are transported by ground ambulance, not by air, with care provided by a single paramedic. An automated device, such as the autoRIC®, could prevent delays or interruptions in care and eliminate the need for dedicated personnel or ongoing provider attention.[7,11,12] Further study of EMS use of an automated device is needed to inform the design and optimize methods for a future U.S.-based trial of the clinical efficacy of RIC administered during ground ambulance transport.

1.6 Dose Rationale and Risk/Benefits

In previously published clinical studies, one cycle of RIC has typically been five minutes of upper arm ischemia, induced by inflating a cuff to 200 mm Hg, followed by five minutes of reperfusion by deflating the cuff. Each 10-min cycle is repeated four times. This dosing regimen was followed in recently completed clinical trials,[22,23] and is being used in the ongoing CONDI2 (NCT01857414) and ERIC-PPCI (NCT02342522) trials. Our study protocol will therefore administer RIC in accordance with these studies using the autoRIC® device, which automates the process.

Based on previous studies, RIC is a safe procedure with minimal risk to subjects across various settings and patient populations. From the Danish trial in which RIC was administered in STEMI patients in the ambulance prior to hospital arrival, Botker et al. reported no local adverse effects, such as pain or thrombophlebitis.[26] In two large RCTs in patients undergoing CABG surgery, one observed no adverse events related to RIC;[23] the other found 5% of the RIC intervention group experienced skin petechiae or arm weakness or altered sensation although none had long-term effects.[22] In a U.S. study of RIC during air medical transport of STEMI patients, only 2% of patients stopped RIC due to discomfort.[38]

Published studies of the autoRIC® device support the safety of this specific device for administering RIC. Two previous studies used this specific automated device to investigate the effect of RIC on coagulation, platelet function, and fibrinolysis in small samples of healthy male volunteers[39] and patients with chronic heart failure.[40] Neither study reported any complications or adverse events related to RIC or the device itself. However, neither study directly evaluated risks to subjects or studied the device in an emergency care setting.

Given the benign nature of the RIC procedure, no serious adverse events are expected as a result of the device. However, the device may result in non-serious adverse events, such as minor arm discomfort, temporary discoloration of the arm or hand, and minor skin bruising or abrasions on the upper arm. These anticipated risks are not expected to have long term consequences and are reasonable in relation to the knowledge gained on the feasibility of RIC and optimal methods for a full-scale clinical trial to help establish long-term benefits.

2 Study Objectives

The overall purpose of this pilot study is to assess the feasibility of the delivery of RIC by EMS in the prehospital setting. To this end, we will conduct a single-arm study of the standard RIC procedure (i.e., up to four cycles of alternating 5-min inflation and 5-min deflation) administered by Orange County (North Carolina) Emergency Services in 50 patients experiencing chest pain or other symptom consistent with cardiac etiology. The investigational autoRIC® device will be initiated by paramedics during ambulance transport, and automated RIC cycles will continue through emergency department (ED) arrival and stay. This pilot study will address the following objectives:

2.1 Primary Objective

Examine the duration of RIC administered in patients having the procedure initiated in the prehospital setting

Hypothesis: Four cycles of RIC will be completed in at least 80% of patients having the procedure initiated.

2.2 Secondary Objectives

The following secondary objectives will inform the design and optimize methods for a future clinical trial:

1. Evaluate patient enrollment and study protocol efficiency, i.e. patient eligibility and participation rates, times to screen, recruit and start the autoRIC® device
2. Assess acceptability of the study protocol by paramedics
3. Determine patient tolerability of the RIC procedure and describe related risks and discomforts

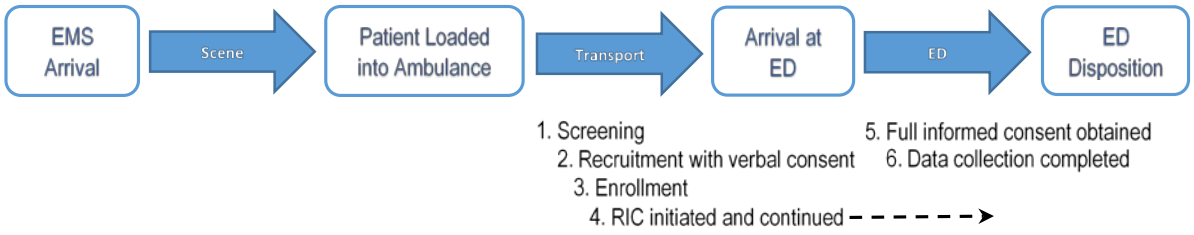
3 Study Design

3.1 General Design

This single-arm, open-label pilot study will enroll 50 patients experiencing chest pain or anginal equivalent symptom requiring a 9-1-1 response to incident scene and ground ambulance transport by Orange County Emergency Services (OCES), the primary EMS provider in the county. Eligible patients will be ≥18 years of age and be transported to the University of North Carolina (UNC) Medical Center, an accredited chest pain center. For this pilot study, patients suspected of STEMI based on the prehospital ECG and thus requiring urgent intervention in the cardiac catheterization lab will be excluded.[1] Detailed subject selection criteria are described in Section 4.

The following diagram (Figure 2) illustrates the overall flow of patient enrollment and major procedural steps during ambulance transport and ED stay.

Figure 2. Diagram of Patient Enrollment and Study Procedures



[1] Although high risk STEMI patients hold the most promise for therapeutic benefit, the aims of this study surrounding feasibility of prehospital RIC can be addressed with a low risk population. By using chest pain patients not suspected of STEMI, we will simulate the prehospital setting expected for an efficacy trial of RIC while allowing adequate time to interview patients in the ED.

3.2 Primary Outcomes

To assess the feasibility of delivering RIC in the prehospital setting, the primary endpoint will be the completion of 4 cycles of RIC without interruption using the autoRIC® device. We will also examine total time (in minutes) and number of cycles that RIC was administered.

3.3 Secondary Outcomes

Secondary Objective #1: Patient enrollment and protocol efficiency

a) Eligibility and participation rates and corresponding reasons for ineligibility and refusal
b) Timing of study procedures
    i) Time to onset of transport from initial arrival on scene
    ii) Time to start screening from onset of transport
    iii) Time to screen, whether eligible or not
    iv) Time to recruit, whether enrolled or not
    v) Time to start the autoRIC® device once consent is obtained

Secondary Objective #2: Paramedic acceptability

a) Paramedics' feedback on the delivery of RIC and other study procedures

Secondary Objective #3: Patient tolerability

a) Documentation of anticipated adverse events including RIC discontinuation due to discomfort
b) Patients' experiences while undergoing the RIC procedure

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Eligible patients will meet the following criteria:

1. Requiring 9-1-1 response to scene[2]
2. At least 18 years of age
3. Experiencing non-traumatic chest pain or anginal equivalent[3] symptom, as defined in OCES "Chest Pain: Cardiac and STEMI" patient care protocol (see Appendix A)
4. Not meeting EMS criteria for a suspected STEMI based on prehospital ECG[4]
5. Systolic blood pressure (SBP) between 100-180 mm Hg
6. Designated for ambulance transport to UNC Medical Center (Chapel Hill, NC)
7. Capable of providing informed consent

4.2 Exclusion Criteria

The following exclusions will be made in the prehospital setting and confirmed prior to recruitment:

1. Unconscious or otherwise in critical condition
2. Lacking capacity to consent to the study[5]
3. Non-English speaking

[2] Does not include non-9-1-1 responses such as interfacility transfers and non-urgent medical transports
[3] Includes pain in other location suggesting cardiac etiology such as arm, shoulder, neck, or jaw; dyspnea; diaphoresis; nausea/vomiting; or dizziness
[4] Defined as 1 mm or greater ST segment elevation in at least 2 contiguous leads or otherwise prompting a prehospital STEMI alert or activation of the cardiac catheterization laboratory
[5] As judged by study paramedic and study coordinator

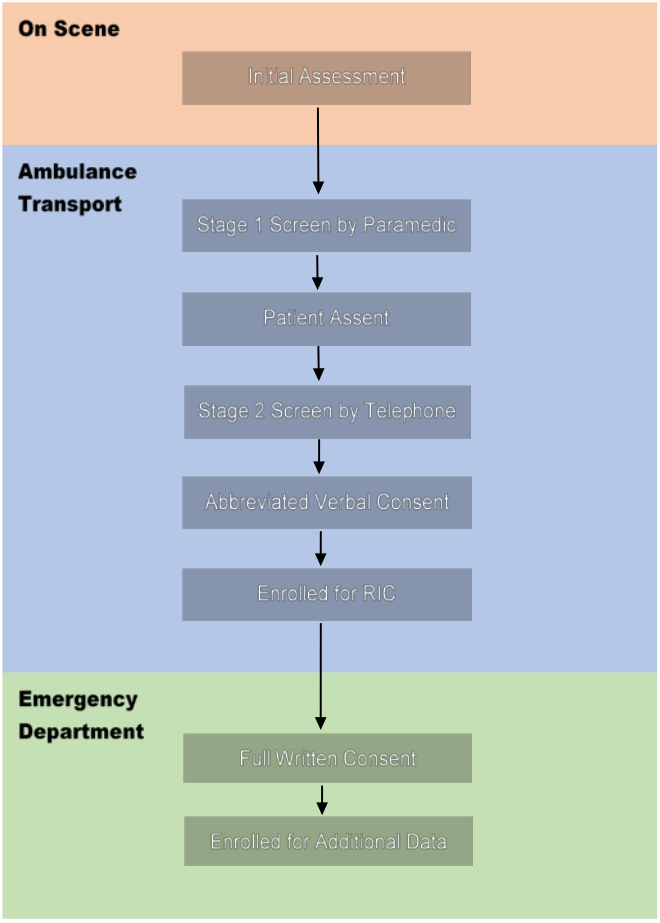
4. Pre-existing condition precluding blood pressure check or use of the autoRIC® at the discretion of the provider or listed here:
    a. Paresis of upper limb
    b. Pre-existing traumatic injury to arm
    c. Presence of an arteriovenous shunt for dialysis
    d. Prior mastectomy
    e. Existing peripheral inserted central catheter line
    f. Arm edema or other indication of upper extremity thrombosis
5. Serial ECG evidence of evolving STEMI

4.3 Subject Recruitment and Screening

Two full-time OCES ground ambulance units that provide advanced life support (ALS) services to the southern part of Orange County and typically transport to UNC Medical Center will be used for this study. Paramedics assigned to these units will be responsible for assessing and screening patients during the enrollment period from 6am-6pm, Monday-Friday. So that arrival to the UNC ED is not delayed, screening and recruitment will not begin until the patient is en route to the hospital and given usual care, at the discretion of the paramedic. Paramedics will assess the patients' capacity to consent for the study following their usual approach to assessing patients' capacity to make medical decisions, e.g. accept or refuse treatment.

In a two-stage screening and recruitment process (Figure 3), the study paramedic will first assess and determine whether the patient meets all eligibility criteria. If the patient is not eligible, the paramedic will document the primary reason(s) on a screener form. If the patient is eligible, the paramedic, using a suggested script (see Appendix B), will offer the patient an opportunity to learn more about the study by telephone call with a study coordinator (SC). If the patient agrees, the paramedic will hand the patient a study information sheet (see Appendix C) and will call the SC or back-up key study personnel using a dedicated cellular telephone. In the second screening stage, the SC will confirm with the paramedic that the patient is eligible. Then the patient will be handed the telephone. The SC, following a script (see Appendix B), will provide basic information about the purpose of the study, RIC procedure, and risks and benefits of participating and will answer any questions that patient may have. To assess consent capacity, the SC will ask the patient to describe the RIC procedure and whether study participation will have any effect on medical care received. A patient with capacity to consent will be invited to participate. If the patient responds in the affirmative, this will be considered verbal consent, and the SC will instruct the paramedics to apply and start the autoRIC® device. This telephonic method to obtain consent in the field is based on a strategy developed and tested in prior prehospital trials by Saver et al.[41,42]

Figure 3. Flow chart of recruitment and enrollment



When the patient and paramedic crew arrive to the ED, providers in the ED will first provide standard care. The SC will collect study forms and other documentation from the paramedic. Once initial care (e.g., provider assessment, repeat ECG, lab draws) is completed and the patient is placed under observation for further work-up, the SC will approach the patient, with approval from the treating physician, to complete the full informed consent process and describe additional data collection including medical record review and abstraction and collection and storage of blood samples for future testing. The SC will assess comprehension based on the patient's ability to restate key study objectives and procedures and anticipated risks and benefits. If the patient consents, both SC and patient will sign two copies of the informed consent form (see Appendix D), one for study documentation and the other for the patient. If the patient refuses, RIC will be stopped and data collected up to that point will be de-identified and retained to address primary and secondary study objectives.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may withdraw from the study at any point without consequence to their future care. If consent is withdrawn while RIC cycles are being administered, regardless of reason, the autoRIC® device will be stopped and removed from the patient. There are no anticipated risks to patients from abrupt termination of the RIC procedure. Care providers (i.e. paramedics or ED physicians) may terminate RIC if the patient becomes severely hypotensive (SBP < 90 mm Hg), experiences an unsafe drop or rise in blood pressure, or for other safety reasons at the discretion of the provider. Discontinuation of RIC prematurely will be documented as a primary endpoint. Specific reason(s) for discontinuation whether related to patient tolerability or safety will be documented to address secondary objectives and will be recorded for adverse event reporting.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Study objectives do not require subject follow-up past EMS response, ambulance transport, and ED stay. Withdrawn subjects will be asked for primary reason(s) for terminating participation in the study.

5 Study Device

5.1 Description

The autoRIC® is a device system that automatically delivers cycles of RIC. Once placed on the upper arm, the programmed device is initiated by pressing a single start button with each cycle consisting of a 5-min period of a cuff inflated to 200 mm Hg followed by a 5-min period of the cuff deflated. The system is programmed to operate a total length of 35 minutes since the final 5-min period of deflation is technically no action or intervention. Additional details of the investigational device are provided in Section 1.2.

5.2 Procedure Regimen

The autoRIC® is programmed to deliver four cycles of RIC with each cycle consisting of a 5-min period of a cuff inflated to 200 mm Hg followed by a 5-min period of the cuff deflated for a total procedure time of 40 minutes. At any time, RIC can be terminated by pressing the stop button or physically removing the cuff-device system from the arm.

For this study population, RIC is not considered a treatment since no clinical benefit is expected in patients not undergoing reperfusion, as in STEMI patients receiving PCI, or otherwise at risk for ischemia-reperfusion injury. Therefore, rather than testing a treatment effect, the autoRIC® in this study is being evaluated for feasibility of prehospital delivery and operational efficiency.

5.3 Method for Assigning Subjects to Treatment Groups

Since this is a single-arm, pilot study, all subjects will receive the study device. There will be no assignment or randomization of treatment groups.

5.4 Preparation and Administration of Study Device

The autoRIC® device will be stored in a locked cabinet at the EMS station while not in use for the study. At the start of each 6AM-6PM enrollment period, the paramedic will ensure the device is fully charged. The charging cradle will be set up in the ambulance unit, and, after each use, the device will be returned to charging cradle. If necessary, up to 3 consecutive patients can be treated on a full charge, but every effort will be made to keep the device fully charged.

The autoRIC® will be administered according to the operator's manual. Briefly, once the paramedic determines the appropriate cuff size, the applicator cuff, with control unit, is placed directly on the upper arm without any clothing, tubing, or other foreign object between the cuff and patient. If IV access has been established in an arm as part of providing usual care, the device will be applied to the opposite arm. Blood pressure measurements, for usual care, will be made in the arm with the IV in place.

Once the device is in place and the paramedic presses the "Start" button, s/he will confirm all LEDs illuminate to ensure the device is working properly. After the fourth and final cuff inflation, the device can be removed from the patient for the final 5-min deflation period. The applicator cuffs are single-use, and therefore, they will be disposed according to OCES and UNC's medical waste policy.

The paramedic will retrieve the device after each use. If the ambulance unit is back in service prior to the completion of four cycles, the device will be returned to the ambulance by the SC or other key study personnel.

5.5 Subject Compliance Monitoring

Device start and stop times will be recorded by paramedic or SC, as appropriate. If the autoRIC® is prematurely terminated for any reason, the number of cycles completed and progress of the current cycle will also be recorded as indicated by LED lights on the device. This information will be captured as the primary study endpoint.

5.6 Prior and Concomitant Therapy

Medications administered by the paramedic will be collected. It is expected these will primarily consist of aspirin and nitroglycerin for management of chest pain.

5.7 Packaging

The autoRIC® devices will be shipped with their standard packaging and product labeling.

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Devices & Supplies

The required number of autoRIC® devices (three total – two for study use and one for training and back-up) will be shipped from the supplier CellAegis Devices, Inc. (Toronto, Canada) to the study PI. Upon receipt of the study devices and supplies, an inventory will be performed, and a device receipt log filled out and signed by the person accepting the shipment. Designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory.

5.8.2 Storage

According to technical specifications, the autoRIC® can be transported and stored in an ambient temperature range of -4 °F to 122 °F and a relative humidity range of 0% to 85%. When not in use, devices will be stored in locked cabinets.

5.8.3 Dispensing of Study Device

Devices will be dispensed to study paramedics by the PI. In a device accountability log, the PI and SC will keep track of each device and document each use including the size of the single-use applicator cuff. Using this log, the study PI and SC will monitor the remaining supply of each cuff size and will re-order as needed.

5.8.4 Return or Destruction of Study Device

At the completion of the study, the autoRIC® devices will be stored in a locked cabinet at the study site. If no future studies are planned, the devices will be shipped back to the supplier CellAegis Devices, Inc.

6 Study Procedures

This study requires a single visit. Table 1 illustrates the flow of study procedures throughout the study visit and additional data collection following the visit. All study procedures involving direct patient interaction will occur in the ambulance and ED. Prior to the onset of subject enrollment, study paramedics will undergo training on the study protocol and standard operating procedures.

6.1 Ambulance Transport

During ambulance transport, the study paramedic will record information on a paper Case Report Form (CRF). The CRF will be pre-populated with a unique subject identifier (ID). The paramedic will document general information, including incident date-time, patient name and contact information, and will also complete the screener. As previously described, eligible patients interested in learning more about the study will be connected to the SC by telephone. After verbal consent is obtained over the telephone, the paramedic will prepare the autoRIC® device (e.g. check battery, determine appropriate cuff size). The device will be placed on the patient and started according to the operator's manual. Along the way, the paramedic will record the time of RIC initiation and other key time points needed to compute secondary endpoints. While RIC is being administered, the paramedic will note observations and feedback on the recruitment process, operating the device, patient safety or adverse events, and any delays incurred due to RIC or other study procedures. If RIC is terminated prematurely, the paramedic will document the primary reason(s).

Table 1. Flow of Study Procedures and Data Collection

Study Procedures	Study Visit		Post-Visit
	Ambulance Transport	Emergency Department	
Standard care (paramedic and ED staff)	X	X	
Screening	X		
Initial verbal consent by telephone	X		
RIC intervention*	X → →	→ → →	
Safety and adverse event reporting	X	X	
Full written informed consent		X	
Blood collection, preparation, and storage		X	
Patient interview		X	
Additional Data Collection			

Medical record review		X
Cardiac monitor report retrieval		X
Blood analysis (post-hoc)		X

*may overlap with other study procedures

6.2 Emergency Department

The SC will meet the paramedic team and patient in the ED. At this point, the paramedic will hand over the CRF to the SC and transfer study responsibilities, including safety and adverse event reporting. After initial ED care and while the patient is under observation and awaiting further work-up, the SC will complete the full informed consent process. This process may occur while the RIC procedure is still in progress. Although the study intervention is already started, the subject will have the opportunity to decline participation in the patient interview; access to medical records and other clinical data; and collection and storage of blood specimens for future testing. The SC will assess comprehension of consent by asking the subject to describe the purpose of the study, foreseeable risks and benefits of study participation, the possibility of unanticipated risks, and other elements of informed consent. No additional study procedures will occur until the consent process is complete and both patient and SC sign necessary consent forms.

After consent is obtained, a blood sample of 15 mL will be collected by Department of Emergency Medicine clinical research staff using existing venous access. When possible, this sample will be obtained with other blood draws taken as part of usual care. Blood for plasma will be collected using an EDTA tube (e.g., BD Vacutainer® plastic blood collection tube). Tubes will be labeled with the date and time of collection and the unique subject ID but no other identifiers. Specimens will be prepared according to standard procedures for separating plasma and will be stored in a -80 °C freezer located in a locked area in the department's research laboratory. No blood testing or analyses will be done under this protocol. In future studies, these samples may be used to investigate biomarkers and molecular pathways involved in the mechanism(s) of RIC.

Using an interview guide, the SC will elicit patient feedback on undergoing the RIC procedure (e.g., "what did it feel like?", "how would you describe to someone else?"). The SC will note subject responses in the CRF.

6.3 Post-Visit

There will not be any post-ED visits required of the subject. All additional study data collected following the study visit will be obtained by the SC or other study personnel via retrospective chart review and will not require subject interaction. Subjects will however be contacted after 48 hours, either by telephone or in-person depending on location, to assess for adverse events related to study participation.

Following the study visit, the SC will enter data from the CRF into a secure, web-based database (Research Electronic Data Capture, REDCap). Additional relevant clinical data from the subject's medical record (e.g. medical history, diagnoses, and lab results) and the EMS patient care report will also be abstracted and entered into the database. Furthermore, automatic reports from the EMS agency's LIFEPAK® 12 cardiac monitor will be retrieved and saved for potential additional analyses of vital signs and ECG patterns. Frozen plasma specimens may be thawed and tested in future research exploring mechanisms of RIC.

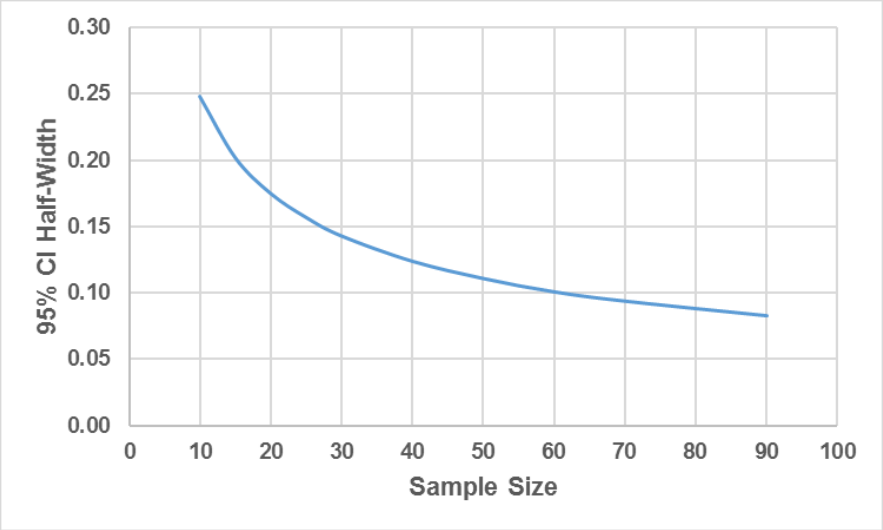
7 Statistical Plan

7.1 Sample Size Determination

Since the primary objective of this pilot study is to assess feasibility and optimize methods, no formal statistical hypothesis testing will be performed. A 5-month enrollment period is appropriate given limited time and resources,

and will be sufficient to enroll the target of 50 patients. This sample size would produce a 95% (confidence interval) CI half width of 0.11 given the frequency of RIC completion is 0.80 (primary hypothesis). Sample sizes larger than 50 provide only marginal gains in precision (Figure 4).

Figure 4. Statistical precision in the primary endpoint by sample size



7.2 Statistical Methods

Summary statistics (e.g., proportions, medians) will be used to characterize the study sample with respect to patient demographic and clinical characteristics and process factors related to the RIC procedure. The primary outcome measure, as previously discussed, will be the frequency (i.e., proportion) of all subjects receiving RIC who completed 4 cycles. The primary hypothesis will be evaluated by comparing the proportion and its 95% CI to the predetermined benchmark of 0.80. Since this is a pilot study to collect feasibility data, no inferential statistical tests will be performed. Descriptive analyses will compare patient characteristics (demographics, medical history, clinical factors) and process measures (timing of study procedures) between RIC completers and non-completers.

Qualitative data from paramedic feedback and patient interviews will be analyzed for general themes regarding key aspects of study methodology. Themes will be derived from qualitative text and related to quantitative demographic and clinical characteristics in a mixed methods analysis using the software MAXQDA (VERBI GmbH, Berlin, Germany). A full analysis plan will be developed in consultation with UNC mixed methods research experts.

7.3 Subject Population for Analysis

For both primary and secondary objectives, any subject consented and enrolled to receive RIC will be analyzed.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form)

- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research,
- Serious (as defined below) "***Serious" is different than "severe" as reported in the CTC criteria that applies a grade to the AE.***

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study visit. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- any of the following important medical events: acute STEMI, severe hypertension (SBP > 200 mm Hg), significant heart block requiring emergency cardiac pacing, cardiogenic shock, cardiac arrest

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance in this patient population. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported will start at the time of verbal consent, include the 40-min RIC procedure, and conclude when the SC completes study procedures in the ED. A subject follow-up contact will be made at 48 hours to assess for adverse events. If a subject expresses RIC-related health concerns at any time, s/he will be connected to a study physician for a telephone assessment and triage which will include a determination of whether re-evaluation in the ED is needed.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained.

Abnormal Laboratory Values
All lab tests conducted during the study visit will be part of the usual care in the ED and not the study procedures. Therefore, any abnormal values will not be reported as AEs. Blood collected for future research may be tested at a later date, and any abnormal values will also not be reportable.

Hospitalization or Prolonged Hospitalization
The majority of subjects, due to their cardiac condition, will be hospitalized. This will not be reported as an SAE. However, a hospitalization or prolonged stay related to participation in the study will be reportable.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions in Section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study Identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Reporting to Study Sponsor

Any study-related unanticipated problem posing risk of harm to subjects or others and any serious adverse event (see Section 8.1) must be reported to the study sponsor-investigator. i.e. PI, by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form must be completed by the SC, study paramedic, or other study staff and provided to the study PI within 24 hours. The PI will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:
Mehul D. Patel, PhD Phone: (919) 843-7307 Fax: (919) 966-3049

Within the following 48 hours, the PI must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study PI.

8.3.2 Reporting to IRB

For reportable deaths, the initial submission to the UNC IRB may be made by contacting the IRB Director or Associate Director. The SAE Form is required as a follow up to the initial submission.

Other Reportable events:
For this clinical study, the following events are also reportable to the UNC IRB:

- Any unanticipated problems involving risk to subjects or others (See Section 8.1)
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.4 Unblinding Procedures

This is an open-label study, so no unblinding procedures will be necessary.

8.5 Stopping Rules

This study does not present potential for serious risk to the health, safety, and welfare of subjects, so no stopping rules will be necessary.

8.6 Medical Monitoring

It is the responsibility of the PI to oversee the safety of the study at his site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 10 Study Monitoring, Auditing, and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious and non-serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the completion of the study. These documents should be retained for a longer period if required by an agreement with the study sponsor or IRB. In such an instance, it is the responsibility of the investigator to inform the study team as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The study PI will ensure that adequate data and safety monitoring information is collected and reviewed according to the study monitoring plan. The focus of monitoring will be adverse event review and reporting, data security

and subject privacy and confidentiality, and study procedure quality control and data completeness and accuracy. The PI will hold weekly meetings with study staff to review and verify these steps.

The PI will allocate adequate time for such monitoring activities. The study investigators and other key personnel will meet biweekly during the enrollment period to review and discuss data and safety monitoring information. In the event of monitoring by the UNC Quality Assurance Office, the PI will also ensure access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Appendix C for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. A separate form for stored specimens with identifiers will be provided to consent subjects to the collection and storage of blood samples for future research.

Under Investigational Device Exemptions (IDE) regulations (21 CFR 812), the sponsor-investigator Dr. Patel has determined this medical device study to be a nonsignificant risk and will present this determination to the UNC IRB. Given the minimal risk of the study intervention and limited time to start the procedure prior to ED arrival, the subject must provide verbal consent prior to undergoing RIC. The full written consent of a subject, using the IRB-approved consent form, must be obtained before the subject undergoes remaining study procedures. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

The study is jointly financed through Dr. Patel’s junior faculty development award from the UNC Office of the Provost, internal funds from the UNC Department of Emergency Medicine, and a pilot award from the NC TraCS

Institute (funded through a CTSA grant from NIH's National Center for Advancing Translational Sciences). Additional funding support has been requested in a pilot grant application to the Falck Foundation (Aarhus, Denmark). These funds will be used to purchase devices and other supplies and cover other study expenses. CellAegis Devices, Inc. provides discounted prices on autoRIC® devices and cuffs to researchers. Otherwise, no industry funding is supporting this study.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of North Carolina investigators will follow the University conflict of interest policy. Any potential conflicts of interests will disclosed in the UNC certification process.

13 Publication Plan

The sponsor-investigator Dr. Patel holds primary responsibility for the publication of the results of the study. Findings from the study will be shared in invited seminars, conference presentations, and peer-reviewed publications. In compliance with current NIH policy, this pilot study will also be registered at ClinicalTrials.gov no later than 21 days after enrolling the first subject. Furthermore, summary results will be submitted no later than one year after the primary completion date, i.e., the date that the final subject received the study procedure.

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15 Appendices

Appendix A: Orange County Emergency Medical Services 2016 Chest Pain Protocol

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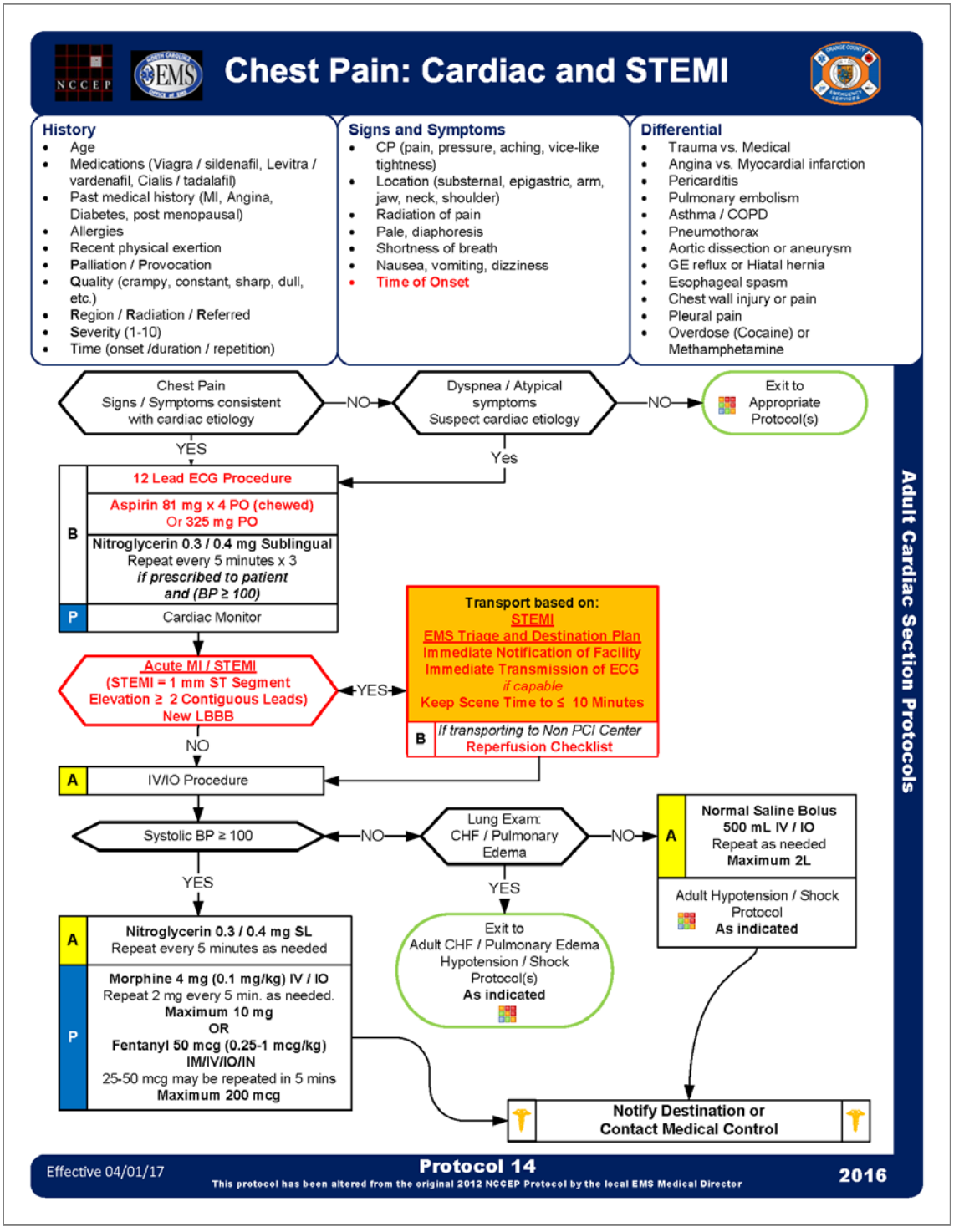

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Chest Pain: Cardiac and STEMI

Adult Cardiac Section Protocols

Notes:

I Lateral	aVR	V1 Septal	V4 Anterior
II Inferior	aVL Lateral	V2 Septal	V5 Lateral
III Inferior	aVF Inferior	V3 Anterior	V6 Lateral

SITE	FACING	RECIPROCAL
SEPTAL	V1, V2	NONE
ANTERIOR	V3, V4	NONE
ANTEROSEPTAL	V1, V2, V3, V4	NONE
LATERAL	I, aVL, V5, V6	II, III, aVF
ANTEROLATERAL	I, aVL, V3, V4, V5, V6	II, III, aVF
INFERIOR	II, III, aVF	I, aVL
POSTERIOR	NONE	V1, V2, V3, V4

Pearls

- **Recommended Exam: Mental Status, Skin, Neck, Lung, Heart, Abdomen, Back, Extremities, Neuro**
- **Items in Red Text are the key performance indicators for the EMS Acute Cardiac (STEMI) Care Toolkit**
- **Avoid Nitroglycerin in any patient who has used Viagra (sildenafil) or Levitra (vardenafil) in the past 24 hours or Cialis (tadalafil) in the past 36 hours due to potential severe hypotension.**
- **Patients with STEMI (ST-Elevation Myocardial Infarction) or positive Reperfusion Checklist should be transported to the appropriate facility based on STEMI EMS Triage and Destination Plan.**
- **For patients that meet STEMI criteria, limit interventions on scene to reduce time to cath lab.**
- **If CHF / Cardiogenic shock resulting from inferior (II, III, aVF) MI, consider Right Sided ECG (V3 or V4). If ST elevation noted, nitroglycerin and / or opioids may cause hypotension requiring normal saline boluses.**
- Best practices involve taking serial EKGs for dynamic changes. Consider taking a right-sided and posterior 12-lead EKG, if applicable.
- Titrate oxygen administration for an Sp02 between 94 – 99%
- If patient has taken nitroglycerin without relief, consider potency of the medication.
- Monitor for hypotension after administration of nitroglycerin and narcotics (Morphine, Fentanyl, or Dilaudid).
- Nitroglycerin and opioids may be repeated per dosing guidelines.
- Diabetics, geriatric and female patients often have atypical pain, or only generalized complaints.
- Document the time of the 12-Lead ECG in the PCR as a Procedure along with the interpretation (EMT-P.)
- **EMT-B may administer Nitroglycerin to patients already prescribed medication. May give from EMS supply.**

Disposition:

EMS Transport: ALS: All except listed those listed below
BLS: Obvious chest wall pain with identifiable non-cardiac origin and SaO2 > 94%
MD Within 4 Hours: Isolated chest wall pain associated with injury and SaO2 > 94%

Revised 02/06//2017

Protocol 14

This protocol has been altered from the original 2012 NCCEP Protocol by the local EMS Medical Director

2016

Appendix B: Suggested Recruitment Scripts

Paramedic Script:
It looks like you may qualify for a pilot study evaluating a technique called remote ischemic conditioning, or "RIC" for short. If you would like more information about the study, I will call the study coordinator/investigator who will explain the study and go through this information sheet with you. While you are on the phone, I will be providing usual care. Is it okay with you if I call the study coordinator so they can tell you more about the study?

Telephone Script:
Hello, my name is _____. I'm a study coordinator/investigator in the UNC emergency department. Thank you very much for wanting to learn more about our study. I understand you are having _____ symptoms. Is that correct?

You are eligible to participate in a pilot study to help understand a technique known as remote ischemic conditioning, or RIC for short. RIC is a simple, non-invasive procedure where a cuff placed on your upper arm is automatically inflated and deflated using a special medical device. You may not benefit from this procedure, but your participation will help us learn more about RIC, and this valuable knowledge will be used in future studies of the benefits of RIC. Previous studies of RIC have shown no serious adverse events or safety risks. The inflation of the cuff however may be uncomfortable. Your participation is voluntary, and regardless of your decision, you will continue to receive the usual care. Also, if you decide to participate, you're free to withdraw for any reason at any time. Thank you for considering. Do you have any questions on the study that I may be able to answer at this time?

Can you describe the procedure that you will receive if you agree to participate in this study?

Will you receive medical care from the paramedic if you don't agree to participate?

Do you wish to participate in our study?

Thank you again for your time. Please hand the phone back to the paramedic.

Appendix C: Sample Patient Information Sheet

UNC SCHOOL OF MEDICINE

Patient Information Sheet Version X
Approved by UNC IRB – Study #17-0287

Prehospital RIC Pilot Study

Official Title: A pilot study of the feasibility of prehospital delivery of remote ischemic conditioning by emergency medical services in chest pain patients

Principal Investigator: Mehul D. Patel, PhD, Research Assistant Professor, Department of Emergency Medicine, UNC-Chapel Hill, Email: mehul_patel@med.unc.edu, Phone: (919) 843-7307

You are invited to participate in a research study. Before you decide, it is important for you to understand why the study is being done and what it will involve. The following are basic questions you may have about the study and some brief answers. Please ask additional questions if anything is not clear or if you would like more information.

What is the purpose of the study?


The autoRIC® Device

We are interested in better understanding a technique known as remote ischemic conditioning (RIC). RIC is a simple, non-invasive procedure where a cuff placed on the upper arm is automatically inflated and deflated using a special medical device (pictured to the right).

We are conducting a pilot study, and rather than testing whether RIC works, we are evaluating the duration that it can be administered when started in the ambulance. We would also like to better understand how it feels to patients such as yourself.

What will happen to me as part of the study?

If you decide to participate, the paramedic will place the device on your arm and start it. After which, you will receive usual care. When you arrive at the emergency department, you will receive usual care. Once the treating physician allows it, I will speak with you about next steps.

Does RIC work?

There is some evidence that RIC can save the lives of patients having a heart attack. However, larger, better designed clinical trials are needed to establish the benefits of RIC. Although you are not the type of patient who could benefit, your participation will help us learn more about RIC, and this will be valuable knowledge for future studies.

Are there any risks to me?

RIC is a simple, non-invasive procedure, and previous studies have shown no serious adverse events or safety risks. The inflation of the cuff however may cause some discomfort or even temporary bruising although it will not cause any permanent damage. Your participation is voluntary, and if you decide to participate, you're free to withdraw for any reason at any time.

What if I decide NOT to participate?

If you decline to participate, you will receive the same standard care throughout the ambulance ride and in the hospital. If you decide to withdraw at any point for any reason, your care will not be affected. We will use data collected up to the point of withdrawal, unless you ask us not to.

Appendix D: Sample Informed Consent Form

CONSENT FORM AND AUTHORIZATION FOR DISCLOSURE OF PROTECTED HEALTH INFORMATION

Mehul Patel, Ph.D. in the Department of Emergency Medicine at the University of North Carolina at Chapel Hill is engaged in research to better understand a procedure known as remote ischemic conditioning (RIC) in patients transported by ambulance. This investigational study is known as:

A pilot study of the feasibility of prehospital delivery of remote ischemic conditioning by emergency medical services in chest pain patients

You have been invited to participate in a research study. Before you decide, it is important for you to understand why the study is being done, what it will involve, and what are the potential risks or benefits to you. The following information is being provided so you can decide with confidence whether or not to participate in this study. Please read this information carefully and ask as many questions as you like before deciding whether you want to take part.

STUDY DESCRIPTION:

The purpose of this research study is to better understand a technique known as remote ischemic conditioning, or RIC for short. RIC is a simple, non-invasive procedure where a cuff placed on the upper arm is inflated to temporarily cut off blood flow in the arm and then deflated to restore blood flow. This process is typically repeated up to four cycles. This study uses an investigational medical device called the autoRIC® (CellAegis Devices, Inc., Toronto, Canada) to automatically administer the RIC cycles.

There is evidence to suggest that RIC can benefit patients having a major heart attack. However, larger, better designed clinical trials are needed to establish the therapeutic benefits of RIC. Although you are not the type of patient that is expected to benefit from RIC, your participation will help us learn more about it.

This pilot study, rather than testing the benefits of RIC, is evaluating the feasibility of starting RIC in the ambulance and continuing the procedure for all four cycles in patients such as yourself. Approximately 50 patients will participate in this study. Valuable knowledge gained from these participants will significantly strengthen future clinical studies.

STUDY PROCEDURES:

Should you decide to participate in the remainder of the study, you will be interviewed during your stay in the Emergency Department (ED). The interview will consist of open-ended questions regarding the RIC procedure and general aspects of the study. This interview will require about 10-15 minutes of your time and will not interfere with your medical care while in the ED. You may refuse to answer any questions.

Clinical research staff will also collect a blood sample (approximately one tablespoon) from you for future testing. When possible, this blood sample will be obtained with other blood draws taken as part of usual care. In the future studies, this sample may be used to look for proteins, enzymes, or other molecules associated with RIC so that we may learn more about how it works. For the time being, your blood sample will be stored indefinitely in a lab freezer within a locked space. Your frozen specimen will be coded and will not identify you. You will not be given any information about the results of the any future blood testing. The results would not be useful to you or your doctors. Additional description of the collection and storage of a blood sample for future testing will be provided in a separate form. You will be given the opportunity to consent to or refuse this piece separately.

Your participation in the study is limited to the ambulance transport and ED stay. However, members of the research team may access and examine your medical records for relevant clinical information about you. Your data will be stripped of any personally identifying information and will be kept confidential throughout the course of the study. There are no follow-up visits required of you though a research team member will attempt to contact you after 48 hours, either by telephone or in-person if you are still in the hospital, to ask about how you are doing.

FORESEEABLE RISKS AND DISCOMFORTS:

RIC is a safe procedure. It has been carried out in thousands of patients in previous studies with no reports of serious adverse events or safety risks. However, some patients have reported minor pain and discomfort due to the inflation of the cuff. Also, in rare cases, there may be some small red spots on the skin caused by the inflated cuff bursting blood vessels in the skin. This is known as skin petechiae and may last for a few days. Skin petechiae does not cause permanent harm or damage.

With any research study, there is the risk that health information about you could be disclosed. The research team have worked to minimize this risk to confidentiality in several important ways:

1. Information collected about you for this study will never be reported using identifying information, such as your name. Information will only be reported anonymously, and about the whole group of patients in the study.
2. The information that we collect about you will be labeled with an identification number only, rather than your name. All paper forms and other information about you will be stored in locked file cabinets with specially made keys in the research office. Any forms that link your name to your study number will be stored in a separate locked cabinet from the information collected about you.
3. Information stored on computer will be kept on servers at the Department of Emergency Medicine at the University of North Carolina, Chapel Hill. Access to the data will be password protected and the servers themselves are behind a firewall and kept in a locked office.
4. Paper forms and electronic data will only be accessible by key members of the research team and will not be shared outside the team.

BENEFITS OF RESEARCH:

You are not expected to receive any personal benefit for being a part of this pilot study. Your participation will help us learn more about how RIC is administered in the ambulance and ED. This is important information that will help us to test the clinical benefit of RIC in future studies.

ALTERNATIVE MEDICAL TREATMENTS:

You do not have to participate in the study to receive care for your current condition. Appropriate medical treatments will be provided to you regardless of your decision to participate.

DISCLOSURE AND CONFIDENTIALITY OF RECORDS:

As mentioned above, several important measures will be taken to maintain the confidentiality of your medical records. However, this information may be disclosed and used by the following or their representatives:

- Study investigators
- UNC Hospital
- UNC IRB
- US FDA
- NIH
- Other government agencies when required by law

Disclosure or use of your records could be, for example, to assure compliance with the study protocol or to provide protection to you as a study participant. There is no expiration date for the use of your records from the study. Any information disclosed to the parties identified above may be re-disclosed by them; however, such re-disclosure is not under the protection of this Consent and Authorization.

COMPENSATION IN CASE OF INJURY:

Should inadvertent injury or damage result from your participation in this study, there are no designated funds provided for subsequent medical care or compensation by either the research study or UNC Hospital. However, you do not waive any legal rights by signing this consent form.

VOLUNTARY PARTICIPATION AND WITHDRAWAL:

Your participation is voluntary, and you may discontinue participation at any time. Refusal to participate or withdrawal will involve no penalty or loss of benefits to which you are otherwise entitled, including medical care at UNC Hospital. However, if you do not agree to sign this Consent and Authorization form, you will not be permitted to participate in this study.

If you decide to withdraw from the study, you must provide a written statement of your choice to withdraw. However, where the study has relied on your consent and authorization up to that point, your consent and authorization cannot be withdrawn.

The study investigators may remove you from this study without your consent for any appropriate reason, which will be explained to you.

STUDY SPONSOR AND FUNDING:

This is an investigator-sponsored study, which means the principal and co-investigators have planned the entire study and are responsible for all aspects of it. The study is jointly funded by the UNC Department of Emergency Medicine and the North Carolina Translational and Clinical Sciences (NC TraCS) Institute. No industry funding is supporting this study.

CONTACT INFORMATION:

You may contact the Principal Investigator, Dr. Mehul Patel, at mehul_patel@med.unc.edu or (919) 843-7307 to answer any questions you might have about your study participation or in case you think you may have any research related injuries.

If you have any questions or concerns about your rights as a research subject, you may contact, anonymously if you wish the UNC Office of Human Research Ethics at IRB_Subjects@unc.edu or (919) 966-3113.

STATEMENT OF VOLUNTARY PARTICIPATION:

I have read the above, have asked questions and have received answers about this study to my satisfaction. I understand what I have read and willingly give my consent to participate in "**A pilot study of the feasibility of prehospital delivery of remote ischemic conditioning by emergency medical services in chest pain patients**." I understand that I will receive a signed copy of this document. I further authorize the use or disclosure of my health and personal information contained in records as described above.

_____ _____

Signature of Research Participant Date

_____

Printed Name of Research Participant

_____ _____

Signature of Research Team Member Obtaining Consent Date

_____

Printed Name of Research Team Member Obtaining Consent